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VIA CM/ECF & HAND DELIVERY

The Honorable Leonard P. Stark
United States District Court for the District of Delaware
J. Caleb Boggs Federal Building
844 N. King Street
Wilmington, DE 19801-3568

Re: ***Avanir Pharmaceuticals, Inc., et al. v. Actavis South Atlantic LLC, et al.,* C.A. No. 11-704-LPS (cons.)**

Dear Judge Stark:

Pursuant to the February 25, 2014 Order (D.I. 475), I write on behalf of Defendants to address the impact of the Federal Circuit's decision in *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013) (*Galderma II*).[1] The decision in *Galderma II* reinforces the conclusion that the patents-in-suit here are invalid. In previous briefing, Defendants pointed out factual differences between the present case and *Galderma I* that undermine Plaintiffs' heavy reliance upon it.[2] *See* D.I. 450 at 12-14. Those factual differences remain after the majority opinion in *Galderma II*. Yet, even without *Galderma II*, Plaintiffs failed to overcome Defendants' clear and convincing evidence of invalidity.

Galderma claimed a concentration of 0.3% of adapalene selected from the prior art, which disclosed a preferred range of 0.01-1.0%. *See Galderma II*, 737 F.3d at 736-37. Here, Plaintiffs similarly claimed a dosage of 10-30 mg Q (and ratios of DM:Q) selected from the prior art, which disclosed 5-50 mg Q (and the claimed ratios of DM:Q). *See, e.g.*, D.I. 429 at 11-17. Plaintiffs' claimed invention is disclosed in the prior art, both in Example 2 of the '248 patent (teaching a specific blood level for treatment of PBA) and in the overlapping ranges of DM and Q taught in prior art, such as the Yakatan Abstract. *See, e.g.*, D.I. 429 at 11-17. Thus, Plaintiffs' routine dosage optimization is obvious.

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[1] Requests for rehearing and rehearing *en banc* are now pending. *See Galderma Labs., L.P. v. Tolmar, Inc.*, No. 2013-1034, D.I. 47 (Fed. Cir. Jan. 31, 2014).

[2] Plaintiffs rely heavily on *Galderma I* in their pre- and post-trial briefs. *See, e.g.*, D.I. 404, Ex. 6 ¶ 107; D.I. 432 at 14, 15; D.I. 446 at 16, 19, 25, 27-28, 30 n.20; D.I. 449 at 2, 6 (citing *Galderma Labs., L.P. v. Tolmar, Inc.*, 891 F. Supp. 2d 588 (D. Del. 2012) (*Galderma I*)).

Galderma II has a significant impact on several arguments advanced by Plaintiffs. In particular, *Galderma II* provides important guidance relevant to Plaintiffs' legal and factual arguments concerning (1) lack of motivation to combine; (2) teaching away; (3) unexpected results; and (4) commercial success.

First, *Galderma II* confirms that obviousness need not be predicated on a motivation to modify a specific prior art embodiment or to achieve what the inventor subjectively sought. *Galderma II*, 737 F.3d at 737.

Second, *Galderma II* confirms that to teach away, the prior art must "criticize, discredit, or otherwise discourage investigation," and that a description of what is believed to be optimal or standard does not teach away. *Id.* at 738-39.

Third, *Galderma II* confirms that "[u]nexpected results that are probative of nonobviousness are those that are different in ***kind*** and not merely in ***degree*** from the results of the prior art." *Id.* at 739 (emphases added) (internal quotation marks omitted).

Fourth, *Galderma II* confirms that the mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug is not probative of commercial success, and that commercial success evidence is of "minimal probative value" where a patent pre-dating the patents-in-suit blocked market entry of competing products. *Id.* at 740-41.

As explained below, *Galderma II* directly refutes arguments advanced by Plaintiffs on each of the above issues.

A. Plaintiffs' lack of motivation argument contradicts *Galderma II*.

Plaintiffs attempt to resurrect the now-defunct "teaching, suggestion, or motivation" test to argue that Defendants must provide an explicit motivation in the prior art to optimize the Q dosage and to combine references. *E.g.*, D.I. 432 at 1; D.I. 449 at 1-2 (citing *Galderma I*). As explained in Defendants' post-trial briefing, Plaintiffs' demand for an explicit motivation in the prior art "invite[s] this Court to commit reversible error." D.I. 444 at 1.

In *Galderma II*, the Federal Circuit found that it was legal error to require the patent challenger "to provide motivation in the prior art" to arrive at the specific claimed amounts of drug starting with the prior art product that included that drug. *Galderma II*, 737 F.3d at 737. "Nothing in the statute or our case law requires [the patent challenger] to prove obviousness by starting with the prior art commercial embodiment and then providing motivation to alter that commercial embodiment." *Id.* (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007)). Here, Plaintiffs' allegation that Defendants failed to satisfy their rigid motivation test is immaterial to the obviousness inquiry, and their contention that there was a lack of motivation to combine the prior art is factually incorrect. In fact, Defendants offered ample evidence of motivation to modify and combine their cited references. *See, e.g.*, D.I. 429 at 8-11; D.I. 444 at 3-9; D.I. 450 at 7-12. Further, from a common-sense perspective, it would be obvious to try to lower the dosage of a potentially dangerous drug, like Q. *See* D.I. 444 at 4-5.

Plaintiffs' argument that a skilled artisan would have no motivation to lower the dosage of Q because the "optimal" dosage of 50 mg had already been discovered (*see* D.I. 432 at 7-8; D.I. 446 at 25-26) is also incompatible with *Galderma II*'s guidance that neither the motivation nor the avowed purpose of the patentee controls. *Galderma II*, 737 F.3d at 737-38. As Defendants have stressed (*e.g.*, D.I. 450 at 7, 17-18), the fact that Plaintiffs' scientists may have believed that 50 mg/day of Q was needed is irrelevant. The evidence shows that the claimed daily dosage of Q and ratios of DM:Q would have been obvious to one of ordinary skill. *See, e.g.*, D.I. 429 at 5-21. In *Galderma II*, the Federal Circuit accepted the finding that not just the patentee, but "many skilled artisans believed at the time of the invention that 0.1% was the optimal concentration." *Galderma II*, 737 F.3d at 736. Galderma argued that the 0.3% concentration was nonobvious because "0.1% was considered the optimal adapalene concentration for the treatment of acne." *Id.* at 737. Yet, the Federal Circuit found an "optimal dosage" is irrelevant to the obviousness analysis: "A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions"; it does not teach away from the claimed invention. *Galderma II*, 737 F.3d at 739.

Plaintiffs erroneously suggest that the patentees' subjective belief that they had optimized the dosage of Q forecloses any finding that a lower amount of Q could ever be obvious:

> The inventors' subjective belief that they successfully optimized the risk/benefit ratio is telling. *See Galderma*, 891 F. Supp. 2d at 642 n.10 ("[T]hese references demonstrate that when [the inventors]—the world's foremost expert with respect to adapalene—attempted such optimization it arrived at 0.1% adapalene as the optimal concentration, and not 0.3%."). Here, like in *Galderma*, the inventors—indisputably the only people in the world with experience developing a DM/Q product for the treatment of PBA—attempted dose optimization and came out with something other than the claimed inventions [of 10-30 mg Q].

D.I. 446 at 25-26 (citations and footnotes omitted). But here, as in *Galderma II*, a subjective belief in "optimal dosages" is irrelevant to obviousness from the viewpoint of a person of ordinary skill.

The same logic applies to Plaintiffs' reliance on Dr. Smith's subjective belief that 100 ng/ml was the optimal blood level for DM. *See* D.I. 432 at 12-13. Moreover, that subjective belief contradicts Example 2 in his own prior art '248 patent, which shows that DM blood levels as low as 43 ng/ml successfully treated PBA. *See, e.g.*, D.I. 429 at 3, 12-13.

B. Plaintiffs' teaching away argument contradicts *Galderma II*.

Plaintiffs' test for the secondary consideration of teaching away, that "a reference will teach away if it ***suggests*** that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought," is inconsistent with the Federal Circuit's guidance in *Galderma II*. D.I. 446 at 19, 27, 28 (citing a footnote in *Galderma I*). Instead, the Federal

Circuit explained that "[a] reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma II*, 737 F.3d at 738 (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). Plaintiffs offered no evidence that Defendants' cited references criticized, discredited, or discouraged investigation into the invention claimed. To the contrary, the prior art leads one of ordinary skill to the claimed subject matter; there is not even the "suggestion" of discouragement.

C. Plaintiffs' unexpected results argument contradicts *Galderma II*.

Plaintiffs urge, without restriction, that "better efficacy ***and safety***" can prove "the unexpected result of the claimed invention." D.I. 446 at 30 n.20 (citing *Galderma I*) (emphasis in original). Using this improper test, Plaintiffs argue that optimizing Q to a lower dose "resulted in unexpected efficacy and safety in treating PBA." D.I. 446 at 30.

In *Galderma II*, the Federal Circuit explained that "[u]nexpected results that are probative of nonobviousness are those that are '***different in kind and not merely in degree*** from the results of the prior art.'" *Galderma II*, 737 F.3d at 739 (emphasis added) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). "Thus, where an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind." *Id.* Here, the prior art disclosed that DM at less than 50 ng/ml blood level successfully treated PBA. *See, e.g.*, D.I. 429 at 3, 12-13. Plaintiffs' "dosage optimization" and the resulting alleged increased efficacy and safety is, at best a difference of degree, not kind.

D. Plaintiffs' commercial success arguments contradict *Galderma II*.

Plaintiffs use another improper test for the secondary consideration of commercial success: if "generic companies have filed ANDAs seeking to enter the [] market," the product "is a commercial success." D.I. 432 at 15 (citing *Galderma I*). Plaintiffs argue that simply because five generic companies filed ANDAs, Nuedexta must be a commercial success. *Galderma II*, however, makes clear that "[t]he mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims." 737 F.3d at 740. Thus, the mere fact that generic pharmaceutical companies submitted ANDAs is not probative of commercial success. *See id.* at 740-41.

Plaintiffs' argument that Nuedexta is a commercial success because its sales have increased fares no better. *See* D.I. 432 at 14-15. The Federal Circuit in *Galderma II* also explained that "[w]here 'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.'" *Galderma II*, 737 F.3d at 740 (alterations in original) (quoting *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005)). Here, market entry by generic

companies has been precluded by regulatory exclusivities and Plaintiffs' expired blocking patent, the prior art '248 patent. Plaintiffs fought vigorously to extend the term of the '248 patent, but lost. *See Avanir Pharm., Inc. v. Kappos*, No. 1:12-cv-69, D.I. 34 (E.D. Va. Mar. 21, 2012) (denying Plaintiffs' request for a patent term extension). Thus, Plaintiffs' evidence of commercial success is, at best, "of 'minimal probative value.'" *Galderma II*, 737 F.3d at 741 (quoting *Merck*, 395 F.3d at 1376).

E. Defendants' invalidity case here is more compelling than *Galderma II*.

The issue in *Galderma II* was whether there was motivation to select the claimed 0.3% adapalene concentration from the range disclosed by the prior art. *See Galderma II*, 737 F.3d at 737. Galderma argued that selecting the 0.3% concentration was nonobvious because "***increasing*** the dose of adapalene [from the commercial 0.1% product] was likely to ***increase*** the incidence of certain side effects." *Id.* (emphases and bracketed material added). Here, by contrast, the issue is whether it was obvious to ***decrease*** the dose of Q because of the motivation to ***decrease*** the risk of side effects. *See* D.I. 450 at 14. In *Galderma II*, the Federal Circuit found that the prior art, showing that an increase in concentration from 0.03% to 0.1% resulted in an increase in side effects, was not probative on the issue of the expected side effects of a 0.3% composition nor did it teach away from the claimed invention or discourage the use of 0.1%. *See Galderma II*, 737 F.3d at 737. Here, the motivation to decrease the dose of Q—a known, powerful drug—is common sense; even a layman would expect reduced side effects with a reduced dosage. *See, e.g.*, D.I. 429 at 8-10; D.I. 450 at 8-12. Thus, the present case is more straightforward than *Galderma II*.

F. Conclusion

Galderma II reinforces Defendants' case, and demonstrates various errors in Plaintiffs' non-obviousness arguments.

Plaintiffs have already had the benefit of 17 years of excluding others from the market with their expired '248 patent. *See* D.I. 429 at 2-3. That patent claimed a DM/Q combination for treating PBA, and was listed in the Orange Book as covering Nuedexta until it expired. *See Galderma II*, 737 F.3d at 735 (noting the significance of a prior art patent having been listed in the Orange Book). Here, Plaintiffs are not entitled to 20 more years of keeping others off the market based on nothing more than selecting a lower dosage of the same drug from their own prior art to treat the same disease.

Respectfully,

/s/ Steven J. Fineman

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cc: Counsel of Record (via CM/ECF)